Pregnancy outcomes in patients with systemic lupus erythematosus with or without a history of lupus nephritis

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Abstract

Background. Pregnancy is an important issue for many women with systemic lupus erythematosus (SLE). This study examined maternal and fetal outcomes among SLE women with or without a history of lupus nephritis (LN).

Methods. We retrospectively analyzed 98 pregnancies in 57 women previously diagnosed with SLE who gave birth at our hospital.

Results. There were 44 pregnancies in women with a history of LN and 54 pregnancies in those without. Fetal loss was observed in 16.1% of SLE pregnancies when excluding induced abortion, and preeclampsia and SLE flare were observed in 12.2% and 6.1% of SLE pregnancies, respectively. No significant differences were evident between women with or without LN in rate of fetal loss, preeclampsia or SLE flare. Women with a history of LN exhibited a significantly shorter duration of gestation (37.0 weeks vs. 38.4 weeks, P=0.006) and lower birth weight (2484 g vs. 2746 g, P=0.007) than those without LN. Multivariate analysis revealed glucocorticoid dose but not history of LN, as an independent risk factor for preterm delivery and low birth weight.

Conclusion. This study was unable to conclude that a history of LN predicted pregnancy outcomes among SLE women. Instead, a higher dose of glucocorticoid at conception was unexpectedly associated with preterm delivery and low birth weight. Further studies are awaited to verify the relationship.

Keywords systemic lupus erythematosus, lupus nephritis, pregnancy, preterm birth

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune and hormone-dependent disease that commonly occurs in women of reproductive age [1]. Pregnancy is an important issue for many SLE women, because SLE has been shown to have a high impact on maternal and fetal outcomes [2]. SLE mothers show worse pregnancy outcomes than the general population; such as increased rates of preeclampsia, fetal loss, preterm delivery, and fetal growth restriction [2]. In addition, hormonal and immune system changes in pregnancy may affect disease activity and progression [3]. SLE flare was more frequently observed during pregnancy in SLE mothers, especially with active disease at conception [1].

Lupus nephritis (LN) is a life-threatening complication of SLE [4]. Higher rates of renal involvement have been observed for Asians (21–65% at diagnosis and 40–82% over time) than for Caucasians [5]. Pregnancy with active LN has been reported to be associated with higher incidence of maternal and fetal complications than those with quiescent LN or without renal involvement in SLE mothers in most studies [6-8]. As the treatment of SLE has improved, most women can become pregnant in remission or under conditions of low disease activity. However, previous studies have shown that SLE women with a past history of LN, even in remission or under low disease activity at conception, are at increased risks of maternal and fetal complications compared to those with no history of LN, although conflicting data were reported among different studies [9-13]. In addition, data on pregnancy outcomes in Japanese SLE women remain limited [14-16]. In the current study, we conducted a single-center retrospective analysis to examine maternal and fetal outcomes in SLE mothers with or without a history of LN.

Materials and methods

Participants

This study reviewed the medical records of pregnancy in SLE women who were treated in our department between January 1996 and March 2018. All patients were Japanese and fulfilled at least four of the 1997 American College of Rheumatology classification criteria for SLE [17]. When the patient wanted to have a baby, pregnancy was allowed by the attending physician based on the guidance or guideline of pregnancy for patients with renal disease at that time, if available [18,19]. We defined women who had a history of LN at conception as having renal SLE, and those who did not have a history of LN as having non-renal SLE. Demographic data included age at conception, age at SLE onset,9-1and SLE disease duration before conception. Laboratory data were obtained from medical records at conception and 6 months after delivery. Proteinuria at conception was defined as urinary protein/creatinine > 0.5 g/gCr. A result of ≥1+ on standard urinalysis was also considered to represent proteinuria when quantitative data were not obtained. Doses of glucocorticoid at conception and during pregnancy were also recorded. Histological features of LN were assessed according to the 2003 International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification [20]. We estimated glomerular filtration rate (eGFR) using equations of eGFR for adult Japanese [21].

Clinical assessments

Maternal outcomes were retrospectively analyzed by comparing the two groups of renal SLE and non-renal SLE patients. SLE flare was defined as the reappearance of urinary proteinuria (protein/creatinine ≥0.5 g/gCr), arthritis, malar rash, oral or nasal ulcers, thrombocytopenia, hypocomplementemia, and elevation of anti-DNA antibody. Any symptom of renal or extrarenal disease requiring a change in treatment was considered as representing SLE flare. Obstetric definitions were defined as follows: abortion, abortion at <22 weeks of gestation; stillbirth, abortion at ≥22 weeks of gestation; preterm delivery, birth at <37 weeks of gestation; term birth, birth at 37–42 weeks of gestation. Babies born weighing <2500 g were categorized as low birth weight, and those born weighing 2500–4000 g were

categorized as normal birth weight. Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy [22]. Hypertension was defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or being on antihypertensive therapy at conception.

Statistical analysis

Statistical analysis was performed using EZR version 1.4 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23]. Continuous variables are expressed as median and interquartile range (IQR), while categorical data are expressed are absolute and percentage values (%). Fisher's exact test and the Mann-Whitney U test were used to compare groups. Risk factors were identified using uni- and multivariate logistic regression analysis. Receiver operating characteristic (ROC) curves were constructed to determine maximum sensitivity and specificity. Differences were considered significant for values of $P<0.05$.

Results

Demographic characteristics at conception

We reviewed the records of 111 pregnancies in 70 SLE women. Excluding 13 pregnancies in 13 patients due to new onset of SLE during or after delivery, 98 pregnancies in 57 SLE women who had already been diagnosed with SLE at before conception were retrospectively analyzed. Twenty-seven patients had 1 pregnancy, 21 patients had 2 pregnancies, 8 patients had 3 pregnancies, and 1 patient had 5 pregnancies. Demographic and clinical details in a group of renal SLE and non-renal SLE pregnancies are summarized in Table 1. Median age at conception and median disease duration before conception were similar in both groups. Pregnancies with renal SLE were treated with significantly higher doses of glucocorticoid at conception. Levels of urinary protein at conception were also higher in pregnancies with renal SLE than

in those with non-renal SLE, and absolute levels were not particularly high, even in renal SLE. Systolic and diastolic blood pressure, levels of serum creatinine, CH50, and SLE disease activity index 2000 (SLEDAI-2K), or frequency of anti-DNA antibody did not differ significantly between groups.

At conception, glucocorticoid was used in 91.8% of pregnancies, but no significant difference was observed between renal and non-renal SLE pregnancies. A small number of pregnancies were treated with immunosuppressants. No significant difference was observed between renal and non-renal SLE pregnancies, although tacrolimus tended to be prescribed more frequently in renal SLE pregnancy.

Fate of pregnancy and neonatal outcomes

The fate of pregnancy and neonatal outcomes with or without a history of LN are shown in Table 2. Fetal loss, including natural or induced abortion and stillbirth, was observed in 25.5% of total SLE pregnancies and 16.1% (14 fetal losses out of 87 pregnancies) when induced abortion was excluded. No significant differences were seen in frequencies of natural or induced abortion, stillbirth, or delivery between renal and non-renal SLE pregnancies. Although the frequency of preterm births did not differ significantly, the duration of pregnancies was significantly shorter in renal SLE pregnancies (37.0 weeks) than in non-renal SLE pregnancies (38.4 weeks, P=0.006). Median birth weight was also significantly smaller in renal SLE pregnancies (2484 g) than in non-renal SLE pregnancies (2746 g, P=0.007). Low weight birth tended to be more frequent in renal SLE pregnancies, but the difference was not significant. No cases of neonatal lupus were encountered. Two fetal malformations were observed, comprising absence of ductus venosus in one case, and microtia in the other.

Maternal outcomes

Maternal outcomes are shown in Table 3. The frequency of SLE flare tended to be higher in renal SLE pregnancies, but no significant difference was identified. Preeclampsia developed in 12 pregnancies (7 in

renal SLE pregnancies, 5 in non-renal SLE patients). No significant differences in levels of serum creatinine, eGFR, CH50, or anti-DNA antibody at 6 months after delivery were identified between renal and non-renal SLE pregnancies (Table 3). No women showed deterioration of renal function at 6 months after delivery compared to at conception.

Risk factors for preterm delivery and low birth weight

To identify risk factors for preterm delivery and low birth weight, we compared patient characteristics at conception and events during pregnancy between preterm and term births and between low- and normal-weight births (Tables 4, 5). Glucocorticoid dose at conception was significantly higher and CH50 at conception was significantly lower in women with preterm birth compared to those with full-term birth (Table 4). Glucocorticoid dose at conception was also significantly higher in women with low birth weight compared to those with normal birth weight (Table 5). Cyclosporine A was used more often in women with preterm births than those with full-term birth (6 patients, 30.0% vs. 4 patients, 4.1%, P=0.006), but there were no significant differences for other immunosuppressive drugs (data not shown).

We then determined the risk factors associated with development of preterm delivery and low birth weight using uni- and multivariate analyses (Table 6). The number of outcomes for preterm delivery and low weight birth weight was 20 and 29, respectively. So, we selected 2 variables for multivariate analysis: Renal SLE and glucocorticoid dose, which showed a high P-value by the univariate analysis. Multivariate analysis revealed that the dose of glucocorticoid at conception was an independent risk factor for both preterm delivery (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.12-1.56; P<0.001) and low birth weight (OR 1.30, 95%CI 1.11-1.52; P<0.001). ROC analysis demonstrated that glucocorticoid dose ≥10 mg/day (prednisolone-equivalent dose) at conception predicts both preterm birth (80% sensitivity, 79% specificity) and low weight birth (66% sensitivity, 79% specificity), respectively (Figure 1).

Discussion

This study examined pregnancy outcomes in SLE women and compared these outcomes between women with a history of LN (renal SLE) and those with no history of LN (non-renal SLE). We first showed that the rate of fetal loss, including natural or induced abortion and stillbirth, was 25.5% in total SLE pregnancies and 16.1% after excluding induced abortions. A 1980 study found that rates of fetal loss in women with clinical active LN prior at conception were high, at 44% and 32% when including and excluding induced abortions, respectively [24]. In the same study, rates of fetal loss in women with remission of LN became lower, at 32% and 13%, including or excluding induced abortions, respectively [24]. Improvements in the treatment of SLE and LN have allowed more women to achieve disease remission before conception. Imbasciati et al. also reported a fetal loss rate of 13%, including neonatal deaths and excluding therapeutic abortion in women with pre-existing LN [8]. Mok et al. reported a fetal loss rate of 12% in SLE women, in a population where most patients had inactive SLE [25]. The rate of fetal loss in our study was similar to rates in those later studies [8, 25]. Our study also showed no significant difference in fetal loss between renal and non-renal SLE.

We then demonstrated that 27.4% of SLE deliveries resulted in preterm birth, and 39.7% of SLE deliveries resulted in low birth weight. Previous studies have also showed high frequencies of preterm birth and low birth weight among SLE women [9, 10, 16, 26]. Murata et al. reported higher rates of preterm and low-weight births among SLE pregnancies (n=63) as compared to the general Japanese population (28.6% vs. 4.6%, P<0.001 and 38.1% vs. 8.0%, P<0.001, respectively), using data from women enrolled in the Japan Environment and Children's Study, a nationwide prospective cohort study [16]. However, previous studies showed conflicting data for preterm and low-weight births among women with or without a history of LN. Bramham et al. reported that women with previous LN had a higher rate of preterm delivery than those without previous LN (30% vs. 11%, P=0.029) [11]. Kwok et al. also showed that women with a history of LN had higher rates of preterm delivery and small for

gestational age (60.0% vs. 24.0%, P=0.007 and 46.7% vs. 20.0, P=0.038, respectively) [13]. In contrast, Saavedra et al. reported that rates of preterm and low-weight births did not differ between women with previous LN and women without LN (48.5% vs. 40%, P=0.4 and 28.5% vs. 35%, P=0.06, respectively) [9].

In our study, the duration of the pregnancy was significantly shorter, and neonatal weights were significantly lower in renal SLE pregnancy compared to non-renal SLE pregnancy. Frequencies of preterm and low-weight births tended to be higher in renal SLE than in non-renal SLE, although no significant differences were identified. However, multivariate analysis revealed that dose of glucocorticoid at conception, but not history of LN, was a risk factor for both preterm and low-weight births.

An association between glucocorticoid dose and preterm delivery in SLE women has been reported in some studies [15, 27-29]. Clark et al. reported that more women in the preterm group were taking ≥10 mg/day of prednisolone-equivalents during pregnancy (50.0%), compared to those receiving <10 mg/day (22.2%, P=0.028) [28]. Kobayashi et al. showed a higher frequency of premature delivery in women receiving >15 mg/day of prednisolone-equivalents during pregnancy (60%), compared to women with ≤ 15 mg/day (13.1%, P<0.05) [29]. These studies just described the association between glucocorticoid dose and preterm delivery. Recently, Deguchi et al. conducted a prospective study to determine risk factors for adverse pregnancy outcomes in SLE women. They reported that prednisolone-equivalents >14 mg/day at conception tended to be a risk factor, although no significant relationship was identified (OR 24.3, 95%CI 0.88–666; P=0.059) [15].

In our study, dose of prednisolone-equivalents was identified as a risk factor for both preterm and low-weight births. Furthermore, ROC analysis showed that ≥10 mg/day of prednisolone-equivalents predicts preterm delivery and low-weight birth with high sensitivity and specificity. We do not know why the glucocorticoid dose influences preterm birth and low birth weight. One explanation would be that the

glucocorticoid itself influences pregnancy outcomes. Previous clinical trials have shown that prednisone treatment to women who have autoantibodies and recurrent fetal loss increased the risk of preterm birth compared to women without prednisone therapy [30, 31]. However, the reason why prednisone induces premature birth is unknown. In addition, we do not know whether preterm and low-weight births could be prevented if women were treated with lower doses of glucocorticoids. Further studies are required to clarify the associations between glucocorticoid dose and premature and low-weight births.

Finally, we showed that 12.2% of SLE women had preeclampsia, and 6.1% of SLE women experienced SLE flare in our study. Maternal complications such as preeclampsia, hypertension, and SLE flare are also important in SLE women [8-11, 13, 32]. Preeclampsia is more common in SLE women than in the general population, even when levels of renal impairment were matched [32]. Previous studies have shown some differences between women with or without a history of LN. For example, Kwok et al. showed higher rates of lupus flare (60.0% vs. 24.0%, P=0.007) and preeclampsia (30.0% vs. 8.0%, P=0.042) in women with previous LN than in those without [13]. Ku et al. reported that SLE flares (62.1% vs. 34.3%, P=0.001) and hypertension (37.9% vs. 14.3%, P=0.025) are more often women with a history of LN compared to those without [10]. In contrast, Bramham et al. reported that preeclampsia (28% vs. 16%) and lupus flare (36% vs. 40%) did not differ between women with or without previous LN [11]. In our study, rate of preeclampsia and SLE flare was relatively low and no significant difference was identified in the frequency of preeclampsia. SLE flares tended to be more frequent in women with a history of LN, although the association was not significant.

Some limitations need to be considered when interpreting the results. First, due to the retrospective analysis, histories of early miscarriages prior to visiting an obstetrician were missing. Second, due to the relatively long study period, the treatment strategy has been changed, particularly for selecting immunosuppressants before conception. Third, in our study, only 1 woman was treated with hydroxychloroquine, which was recommended for use during pregnancy [33], because hydroxychloroquine

was approved for use against SLE in 2015 in Japan. Fourth, the dose of corticosteroids was decided by the attending physician. Therefore, the bias would arise because the physicians' decisions were influenced by factors such as disease severity and patient's background.

In summary, we compared pregnancy outcomes in SLE women with or without a history of LN in our department. No significant differences in fetal loss or occurrence of preeclampsia were seen between the two groups. SLE flare tended to be more frequent in women with a history of LN, but the association was not significant. SLE women with a history of LN had a significantly shorter duration of pregnancy and lower birth weight, compared to those without a history of LN. However, multivariate analysis demonstrated the dose of glucocorticoid, but not the history of LN, is an independent risk factor for preterm delivery and low birth weight. Our data showed almost no difference in pregnancy outcomes between SLE women with or without LN when SLE is controlled well with low-dose glucocorticoid.

Ethical standards

This study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the Gunma University Ethical Review Board for Medical Research Involving Human Subjects (approval number, HS2018-278).

Conflict of interest

The authors have declared that no conflicts of interest exist.

Informed Consent

We provided patients with the opportunity to opt-out by displaying an outline of the analysis on the hospital website.

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Figure legend

Fig. 1. Receiver operating curve (ROC) analysis for predicting (A) preterm birth and (B) low birth weight.

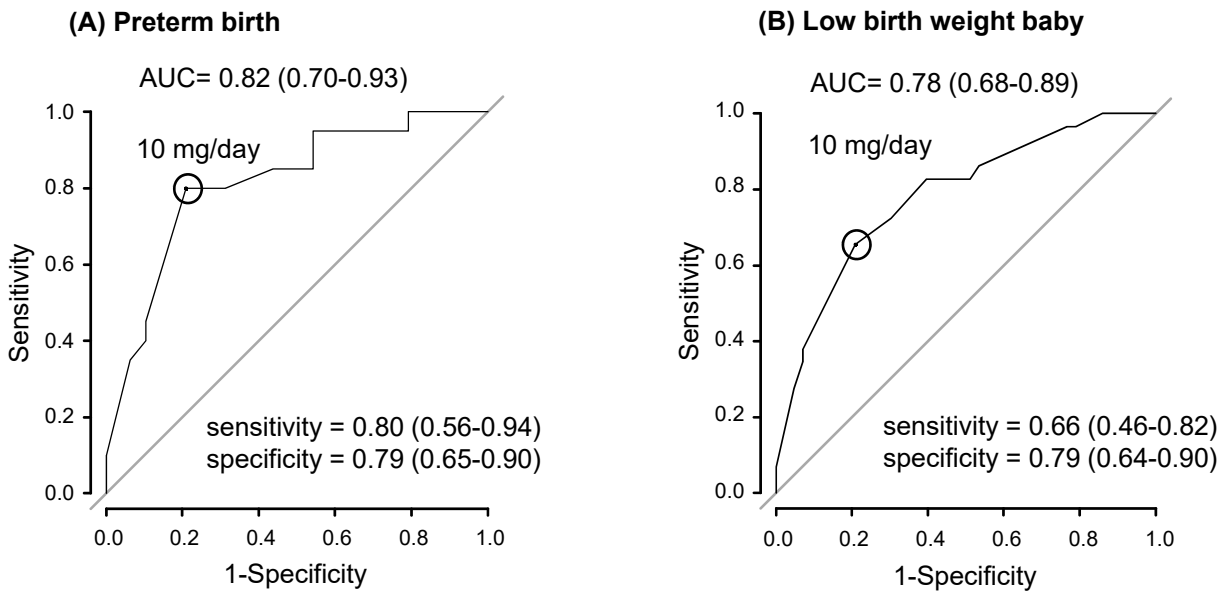
(A) Preterm birth
AUC= 0.82 (0.70-0.93)
10 mg/day
sensitivity = 0.80 (0.56-0.94)
specificity = 0.79 (0.65-0.90)
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
(B) Low birth weight baby
AUC= 0.78 (0.68-0.89)
10 mg/day
sensitivity = 0.66 (0.46-0.82)
specificity = 0.79 (0.64-0.90)
Sensitivity
1-Specificity

Fig. 1

Table 1. Demographic characteristics of renal SLE and non-renal SLE pregnancies at conception.

	Total	Renal SLE	Non-renal SLE	P-value[*1]
Number of pregnancies	98	44	54	
Number of women	57	26	31	
1 pregnancy in this study	27 (47.4%)	14 (53.8%)	13 (41.9%)	0.594
2 pregnancies in this study	21 (36.8%)	8 (30.8%)	13 (41.9%)	
3 pregnancies in this study	8 (14.0%)	3 (11.5%)	5 (16.1%)	
5 pregnancies in this study	1 (1.8%)	1 (3.8%)	0 (0.0%)	
Age at conception (years)	30.0 (26.0-33.0)	30.0 (26.0-33.0)	30.0 (26.3-32.0)	0.678
Age of SLE onset (years)	21.0 (18.0-26.0)	21.0 (16.0-25.3)	21.5 (18.3-26.0)	0.427
Disease duration before conception (years)	7.0 (3.0-12.0)	6.5 (3.8-14.0)	7.0 (3.0-11.0)	0.244
Glucocorticoid[*2] (mg/day)	9.0 (5.0-10.0)	10.0 (7.4-13.0)	7.5 (5.0-10.0)	0.006
SLEDAI-2K	2.0 (0.0-4.0)	2.00 (2.00-4.00)	2.00 (0.00-2.00)	0.008
Hypertention at conception	5 (5.1%)	2 (4.5%)	3 (5.7%)	1.000
Systolic blood pressure	119.5 (108.0-127.0)	121.0 (106.5-126.0)	118.0 (109.0-130.0)	0.521
Diastolic blood pressure	71.0 (63.0-77.0)	71.0 (65.0-77.0)	71.0 (61.0-77.0)	0.634
Serum creatinine (mg/dL)	0.50 (0.43-0.57)	0.50 (0.40-0.57)	0.50 (0.44-0.57)	0.596
eGFR (ml/min/1.73 m^2)	117.2 (99.5-141.4)	121.5 (99.0-143.2)	115.3 (100.2-128.2)	0.647
Urine protein/creatinine ratio (g/gCr)	0.07 (0.05-0.16)	0.15 (0.07-0.27)	0.06 (0.04-0.08)	<0.001
Proteinuria, n (%)	12 (16.9%)	9 (25.7%)	3 (8.3%)	0.063
CH50 (U/ml)	36.9 (28.0-44.2)	34.2 (23.9-40.2)	39.2 (29.4-49.0)	0.055
Positive for anti-DNA antibody	36 (43.9%)	19 (52.8%)	17 (37.0%)	0.182
Sjögren syndrome, n (%)	18 (18.6%)	4 (9.1%)	14 (25.9%)	0.038
Anti-phospholipid syndrome, n (%)	14 (14.4%)	7 (15.9%)	7 (13.0%)	0.775
Previous medication				
Cyclophosphamidem, n (%)	16 (16.3%)	11 (25.0%)	5 (9.3%)	0.053
Mycophenolate mofetil, n (%)	8 (8.2%)	5 (11.4%)	3 (5.6%)	0.461
Azathioprine, n (%)	22 (22.4%)	8 (18.2%)	14 (25.9%)	0.467
Tacrolimus, n (%)	19 (19.4%)	16 (36.4%)	3 (5.6%)	<0.001
Cyclosporin A, n (%)	10 (10.2%)	9 (20.5%)	1 (1.9%)	0.005
Hydroxychloroquine, n (%)	1 (1.0%)	1 (2.3%)	0 (0%)	0.449
Antiplatelet drug, n (%)	21 (21.4%)	8 (18.2%)	13 (24.1%)	0.622
Medication at conception				
Glucocorticoid, n (%)	90 (91.8%)	42 (95.5%)	48 (88.9%)	0.290
Azathioprine, n (%)	7 (7.1%)	3 (6.8%)	4 (7.4%)	1.000
Tacrolimus, n (%)	10 (10.2%)	7 (15.6%)	3 (5.6%)	0.107
Hydroxychloroquine, n (%)	1 (1.0%)	0 (0%)	1 (1.9%)	1.000
Antiplatelet drug, n (%)	18 (18.4%)	7 (15.9%)	11 (20.4%)	0.571

Data are expressed as median (interquartile range) or number (pecentage). SLEDAI-2K, SLE disease activity index 2000

*1 Renal vs. Non-renal

*2 Prednisolone-equivalent dose

Table 2. Fate of pregnacy and neonatal outcome of renal SLE and non-renal SLE pregnancies

	Total (n=98)	Renal SLE (n=44)	Non-renal SLE (n=54)	P-value[*1]
Fate of pregnacy				
Natural abortion, n (%)	13 (13.3%)	6 (13.6%)	7 (13.0%)	0.694
Induced abortion, n (%)	11 (11.2%)	6 (13.6%)	5 (9.3%)	
Stillbirth, n (%)	1 (1.0%)	1 (2.3%)	0 (0%)	
Delivery, n (%)	73 (74.5%)	31 (70.5%)	42 (77.8%)	

	Total (n=73)	Renal SLE (n=31)	Non-renal SLE (n=42)	P-value[*1]
Mode of delivery				
Planned caesarean birth, n (%)	15 (20.5%)	6 (19.4%)	9 (21.4%)	0.236
Emergency caesarean birth, n (%)	23 (31.5%)	13 (41.9%)	10 (23.8%)	
Vaginal birth, n (%)	34 (47.9%)	12 (38.7%)	23 (54.8%)	
Duration of pregnancy (weeks)	38.0 (36.5-39.0)	37.0 (36.1-38.0)	38.4 (37.3-39.2)	0.006
Rates of preterm and term birth				
Preterm birth, n (%)	20 (27.4%)	11 (35.5%)	9 (21.4%)	0.176 [*2]
Full-term birth, n (%)	49 (67.1%)	17 (54.8%)	32 (76.2%)	
Gestational week, unknown, n (%)	4 (5.5%)	3 (9.7%)	1 (2.4%)	
Birth weight (g)	2582 (2287-2888)	2484 (2059-2634)	2746 (2374-3010)	0.007
Rates of low and normal weight birth				
Low birth weight, n (%)	29 (39.7)	16 (51.6%)	13 (31.0%)	0.098 [*2]
Normal birth weight, n (%)	43 (58.9)	15 (48.4%)	28 (66.7%)	
Birth weight, unknown, n (%)	1 (1.4)	0 (0%)	1 (2.4%)	

Data are expressed as median (interquartile range) or number (pecentage).

*1 Renal vs. Non-renal

*2 Without unknown data

Table 3. Maternal outcomes of renal SLE and non-renal SLE pregnancies

	Total (n=98)	Renal SLE (n=44)	Non-renal SLE (n=54)	P-value[*1]
Maternal complications				
Preeclampsia, n (%)	12 (12.2%)	7 (16.0%)	5 (9.3%)	0.662
SLE flare, n (%)	6 (6.1%)	5 (11.4%)	1 (1.9%)	0.087

	Total (n=73)	Renal SLE (n=31)	Non-renal SLE (n=42)	P-value
Postpartum laboratory tests [*2]				
Serum creatinine (mg/dL)	0.57 (0.50-0.64)	0.51 (0.47-0.60)	0.60 (0.52-0.64)	0.084
eGFR (mL/min/1.73 m^2)	99.9 (88.6-112.5)	108.2 (90.4-121.7)	97.6 (87.6-109.1)	0.229
Urine protein/creatinine ratio (g/gCr)	0.08 (0.03-0.20)	0.18 (0.07-0.60)	0.04 (0.03-0.08)	<0.001
CH50 (U/ml)	35.6 (26.8-43.22)	36.0 (24.8-46.0)	35.6 (28.6-40.6)	0.921
Positive for anti-DNA antibody (%)	19 (35.2%)	8 (34.8%)	11 (35.5%)	1.000

Data are expressed as median (interquartile range) or number (pecentage).

*1 Renal vs. Non-renal

*2 At 6 months after delivery

Table 4. Characteristics at conception between preterm and full-term births

	Preterm birth (n=20)	Full-term birth (n=49)	P-value
Age at conception (years)	31.5 (26.8-34.0)	30.0 (26.0-32.0)	0.174
Age at SLE onset (years)	19.0 (18.8-28.0)	22.0 (20.0-26.0)	0.458
Disease duration before conception (years)	7.5 (5.0-13.3)	6.0 (2.0-11.0)	0.088
Glucocorticoid*1 (mg/day)	10.0 (10.0-15.0)	7.3 (5.0-9.0)	<0.001
Renal SLE	11 (55.0%)	17 (34.7%)	0.176
SLEDAI-2K	2.00 (0.00-4.50)	2.00 (0.00, 2.00)	0.202
Hypertention at conception	1 (5.0%)	2 (4.2%)	1.000
Systolic blood pressure	122.0 (113.8-127.8)	118.0 (108.5-126.0)	0.366
Diastolic blood pressure	71.0 (64.5-76.8)	71.0 (60.8-76.8)	0.692
Serum creatinine (mg/dL)	0.52 (0.40-0.59)	0.50 (0.47-0.58)	0.757
eGFR (mL/min/1.73 m^2)	111.2 (98.9-142.8)	114.2 (96.9-123.8)	0.794
Urine protein/creatinine ratio (g/gCr)	0.10 (0.07-0.19)	0.06 (0.04-0.14)	0.036
Proteinuria, n (%)	4 (26.7%)	4 (10.5%)	0.202
CH50 (U/ml)	29.3 (22.3-34.5)	41.6 (33.6-48.3)	0.004
Positive for anti-DNA antibody	5 (31.2%)	19 (43.2%)	0.554
Sjögren syndrome, n (%)	4 (20.0%)	12 (24.5%)	0.764
Anti-phospholipid syndrome, n (%)	4 (20.0%)	5 (10.2%)	0.431

Data are expressed as median (interquartile range) or number (pecentage).
SLEDAI-2K, SLE disease activity index 2000
*1 Prednisolone-equivalent dose

Table 5. Characteristics at conception between low and normal birth weight

	Low birth weight (n=29)	Normal birth weight (n=43)	P-value
Age at conception (years)	28.0 (26.0-32.0)	31.0 (26.5-33.0)	0.224
Age at SLE onset (years)	20.0 (15.0-27.0)	22.0 (19.0-26.0)	0.136
Disease duration before conception (years)	7.0 (2.8-13.3)	6.0 (3.0-11.0)	0.483
Glucocorticoid*1 (mg/day)	10.0 (8.0-15.0)	7.0 (5.0-9.0)	<0.001
Renal SLE	16 (55.2%)	15 (34.9%)	0.098
SLEDAI-2K	2.0 (0.0-4.0)	2.0 (0.0-2.0)	0.373
Hypertention at conception	2 (6.9%)	1 (2.4%)	0.563
Systolic blood pressure	122.0 (113.0-127.8)	120.0 (108.0-126.0)	0.373
Diastolic blood pressure	72.5 (65.5-78.5)	70.0 (60.0-74.0)	0.052
Serum creatinine (mg/dL)	0.50 (0.41-0.60)	0.50 (0.46-0.57)	0.815
eGFR (mL/min/1.73 m^2)	120.9 (95.7-141.8)	112.2 (98.5-124.9)	0.810
Urine protein/creatinine ratio (g/gCr)	0.08 (0.06-0.14)	0.06 (0.04-0.14)	0.412
Proteinuria, n (%)	3 (14.3%)	5 (15.2%)	1.000
CH50 (U/ml)	33.5 (28.3-41.3)	41.6 (31.7-48.3)	0.165
Positive for anti-DNA antibody	11 (47.8%)	14 (36.8%)	0.432
Sjögren syndrome, n (%)	7 (24.1%)	9 (20.9%)	0.748
Anti-phospholipid syndrome, n (%)	3 (10.3%)	6 (14.0%)	0.731

Data are expressed as median (interquartile range) or number (pecentage).

SLEDAI-2K, SLE disease activity index 2000

*1 Prednisolone-equivalent dose

Table 6. Risk factors associated with preterm delivery low and birth weight among SLE women

Characteristics	Preterm delivery				Low birth weight			
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Age at conception (years)	1.10 (0.97-1.25)	0.156			0.95 (0.85-1.06)	0.356		
Age at SLE onset (years)	0.98 (0.90-1.07)	0.632			0.94 (0.87-1.02)	0.141		
Glucocorticoid[*1] (mg/day)	1.34 (1.13-1.58)	<0.001	1.32 (1.12-1.56)	<0.001	1.32 (1.13-1.54)	<0.001	1.30 (1.11-1.52)	<0.001
Renal SLE at conception	2.30 (0.80-6.64)	0.123	1.60 (0.47-5.50)	0.453	2.30 (0.88-6.02)	0.091	1.61 (0.54-4.82)	0.399
SLEDAI-2K	1.18 (0.94-1.49)	0.150			1.07 (0.86-1.33)	0.541		
Hypertension	1.21 (0.10-14.2)	0.879			3.04 (0.262-35.20)	0.374		
Urine protein/creatinine ratio (g/gCr)	1.08 (0.45-2.56)	0.867			0.83 (0.31-2.19)	0.702		
Protenirea	3.09 (0.66-14.50)	0.152			0.93 (0.20-4.39)	0.930		
CH50 at conception (U/ml)	0.93 (0.88-0.98)	0.008			0.97 (0.94-1.01)	0.213		

*1 Prednisolone-equivalent dose